Remarks

Claims 1-7, 16, 23, 26, 31-40, and 41-44 are pending, with claims 1-4 and 41-42 being the independent claims. Claims 3-7, 23, 26, 31, and 33-40 are withdrawn from consideration by the Examiner as being drawn to non-elected inventions. Claims 1-4 have been amended. Support for the amendments may be found throughout the specification, *inter alia*, in the Examples and in the claims as originally filed. Claims 41-44 are sought to be added. Support for these claims may be found at least in paragraphs [00107-00110]. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 102(a)

The rejection of claims 1, 2, 16, and 32 under 35 U.S.C. § 102(a) as allegedly being anticipated by De Groot *et al.*, *Immun. Cell Biol.* 80:255-269 (2002) ("De Groot") is respectfully traversed.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628 (Fed. Cir. 1987); MPEP 2131. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be

so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

De Groot allegedly discloses a method for identifying putative epitopes by identifying the most conserved peptides within a protein from a particular antigen. (OA at p. 3.) Additionally, De Groot is alleged to teach that non-anchor residues of the most conserved sequences can be substituted. As such, the Examiner contends that the method of epitope identification of De Groot "inherently teaches seeking conservative substitutions at the non-anchor positions as the most conserved sequences are chosen." (*Id.*)

De Groot recognizes two methods used for the identification of conserved epitopes: Conservatrix and EpiMatrix. (De Groot at p. 262, col. 1.) EpiMatrix is a software that scores each 8-10-mer peptides for their estimated probability of MHC binding. (*Id.* at p. 260, col. 1.) Conservatrix is described as a sequence matching and counting tool which can compare the 10 amino acid long sequences from different HIV-1 strains and identify broadly conserved peptides. (*Id.* at p. 261, co. 2.) Nowhere in De Groot is it alleged that the term "broadly conserved peptides" equates to a notion that ***every*** non-anchor amino acid is conserved across-clade. The only requirement is that ***the most*** conserved peptides are identified.

In contrast, the methods claimed in the present invention require identification of a variant that comprises ***only conserved*** non-anchor residues. It is also said to be possible to introduce amino acid substitutions at non-anchor positions using Conservatrix. However, De Groot does not require the amino acid substitutions at non-anchor positions to be conservative, as recited in claims of the present invention. In fact, De Groot's silence as to the nature of substitutions allows for non-conservative and semi-conservative substitutions at non-anchor positions. Therefore, all-conserved amino acids in non-anchor positions, as presently claimed, are not inherent features of the epitopes disclosed in De Groot, because this matter is not "necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

Thus, Applicants respectfully assert that De Groot does not expressly or inherently anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103(a)

The rejection of claims 1, 2, 16, and 32 under 35 U.S.C. § 103(a) as allegedly being obvious over De Groot in view of Paul is respectfully traversed.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art are to be

determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). This has been the standard for over 40 years, and remains the law today. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734 (2007). If, after these criteria are considered, the evidence indicates that the claimed invention is obvious over the prior art, it may be said that a *prima facie* case of obviousness have been established.

Applicants respectfully assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness because a person of ordinary skill in the art would not have arrived at the claimed invention based on the teachings of De Groot in view of Paul. As discussed above, and as conceded by the Examiner, De Groot does not disclose a method for identifying an epitope comprising a step of identifying a peptide comprising ***only conserved non-anchor residues***, as required by the present invention.

Paul does not cure the deficiency of De Groot. Paul is alleged to teach that conservative substitutions at TCR contact residues of an epitope result in variants that retain their ability to be recognized by the same TCR. (OA at p. 5.) On the other hand, non-conservative substitutions at TCR contact residues result in loss of reactivity of the TCR for that epitope. As such, the Examiner contends that it would have been *prima facie* obvious to a skilled artisan "to have selected for conservative substitutions at non-anchor residues." (*Id.*)

Applicants respectfully disagree with the Examiner's assessments of Paul. Figure 12 of Paul depicts an HLA-A2-binding epitope. Of the ten amino acids shown, four are indicated as residues that interact with the TCR (residues 4-6 and 8), three are indicated as residues that interact with HLA-A2 (residues 3, 7, and 10), and three residues are not designated as either (residues 1, 2, and 9). Converting to the terminology of the present invention, residues 3, 7, and 10 are "anchor residues", and residues 1, 2, 4-6 and 8-9 are "non-anchor residues". In order to cure the deficiency of De Groot, Paul must teach that ***all*** of residues 1, 2, 4-6 and 8-9 are conservatively substituted, as claimed by the present invention. In contrast, at most Paul suggests introducing conservative substitutions of residues 4-6 and 8. Nowhere in Paul is it taught or suggested that residues 1, 2, and 9 are substituted at all, let alone conservatively.

Even assuming *arguendo* that the Examiner had established a *prima facie* case of obviousness (which Applicants do not concede), the unexpected superiority of the epitopes produced using Applicants' invention over the methodology of De Groot is sufficient to rebut the *prima facie* case of obviousness based on the disclosure of De Groot in combination with Paul. As detailed in the specification of the current application, major challenges exist in developing effective vaccines against infectious agents such as HBV, HCV, HPV, and HIV-1. (*See* "Related Art" section of the specification.) These challenges arise largely from heterogeneity of the individual viruses. Therefore it has proven to be difficult to induce a multi-specific cellular immune response directed simultaneously against multiple viral epitopes. As a result, vaccine containing putative epitopes identified using the methodology described in De

Groot generally will be effective against viruses presenting identical antigens, whereas other viral variants will escape immune recognition.

In contrast, the claimed methodology allows for identification of putative, cross-reacting epitope variants. Stated otherwise, the claimed methodology may be used to identify specific CTL epitopes that are likely to induce ***broad*** immune responses, and the resulting variant may induce a CTL response against many other variants of the peptide epitope. (*See* at least Example 2 of the specification.) Thus, this cross-reactivity of the epitopes produced by claimed methodology is an unexpected and superior property over the methodology disclosed in De Groot.

Since there was no teaching or suggestion of all the claim limitations in De Groot in combination with Paul, a *prima facie* case of obviousness is not established. Furthermore, the claimed invention clearly possesses unexpected superior properties over previously known methodology of De Groot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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